

Optimal Control of Tuberculosis: A Review*

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Abstract We review the optimal control of systems modeling the dynamics of tuberculosis. Time dependent control functions are introduced in the mathematical models, representing strategies for the improvement of the treatment and cure of active infectious and/or latent individuals. Optimal control theory allows then to find the optimal way to implement the strategies, minimizing the number of infectious and/or latent individuals and keeping the cost of implementation as low as possible. An optimal control problem is proposed and solved, illustrating the procedure. Simulations show an effective reduction in the number of infectious individuals.

Keywords: tuberculosis, mathematical models, optimal control.

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1 Introduction

Mycobacterium tuberculosis is the cause of most occurrences of tuberculosis (TB) and is usually acquired via airborne infection from someone who has active TB. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extra-pulmonary TB). Only approximately 10% of people infected with *M. tuberculosis* develop active TB disease. Therefore, approximately 90% of people infected remain

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latent. Latent infected TB people are asymptomatic and do not transmit TB, but may progress to active TB through either endogenous reactivation or exogenous reinfection [52, 53]. Following the World Health Organization (WHO), between 1995 and 2011, 51 million people were successfully treated for TB in countries that adopted the WHO strategy, saving 20 million lives [60]. However, the global burden of TB remains enormous. In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB [60]. The increase of new cases has been attributed to the spread of HIV, the collapse of public health programs, the emergence of drug-resistant strains of *M. tuberculosis* [19, 37, 38] and exogenous re-infection, where a latently-infected individual acquires a new infection from another infectious (see [6, 12, 17] and references cited therein). In the absence of an effective vaccine, current control programs for TB have focused on chemotherapy. Lack of compliance with drug treatments not only may lead to a relapse but to the development of antibiotic resistant TB, called multidrug-resistant TB (MDR-TB), which is one of the most serious public health problems facing society today [27]. The progress in responding to multidrug-resistant TB remains slow. There are critical funding gaps for TB care and control, which is critical to sustain recent gains, make further progress and support research and development of new drugs and vaccines [60].

Mathematical models are an important tool in analyzing the spread and control of infectious diseases [26]. Understanding the transmission characteristics of the infectious diseases in communities, regions and countries, can lead to better approaches to decrease the transmission of these diseases [25, 42, 49]. There are many mathematical dynamic models for TB, see, e.g., [4, 8, 13, 14, 21, 48, 58]. Most models consider that there are two different ways to progress to active disease after infection: “fast progressors” and “slow progressors”. It is also considered that only 5 to 10% of the infected individuals are fast progressors. The remaining are able to contain the infection (latent infected individuals) and have a much lower probability to develop active disease by endogenous reactivation. More recent models also consider the possibility of latent and treated individuals being reinfected, since it was already recognized that infection and/or disease do not confer full protection [57]. Models show that reinfection can be an important component of TB transmission and can have impact on the efficacy of interventions [13, 21, 45, 58]. Here we focus on TB models that consider: development of drug resistant TB [7]; exogenous reinfection [5, 6, 16, 17, 22, 35]; fast and slow progression to infection [5, 6, 16, 22]; post-exposure interventions [22]; immigration of infectious individuals [35]; and time-dependent parameters [59]. These models can be particularly useful in comparing the effects of various prevention, therapy and control programs [25, 32]. Since a variety of these programs are available, it is a natural objective to design optimal programs in terms of some pre-assumed criterion. This calls for the application of optimal control tools [33].

Optimal control has a long history of being applied to problems in biomedicine, particularly, to models for cancer chemotherapy [15, 29, 30, 31, 32, 34, 54, 55, 56]. But until recently, little attention has been given to models in epidemiology [3, 20, 32, 40, 41, 43, 46]. In this paper we review the application of optimal control to

TB mathematical models. The first paper appeared in 2002 [27], and considers a mathematical model for TB based on [7] with two classes of infected and latent individuals (infected with typical and resistant strain TB) where the aim is to reduce the number of infected and latent individuals with resistant TB. Two control strategies are proposed to achieve the objective: a *case finding* control measure, referring to the identification of individuals latently infected with typical TB and who are at high risk of developing the disease and who may benefit from prevention therapy (reducing the number of latent individuals that develop the disease) [27, 39]; and a *case holding* control, representing the effort that prevents the failure of the treatment in the typical TB infectious individuals and referring to activities and techniques used to ensure regularity of drug intake for a duration adequate to achieve a cure (reducing the incidence of acquired drug-resistant TB) [11, 27]. In [24] the authors consider the problem of minimizing the number of infectious individuals with a control intervention representing the effort on the prevention of the exogenous reinfection. The authors of [35] propose the implementation of a *case finding* control, representing the fraction of active infectious individuals that are identified and will be isolated in a facility, for an effective treatment and prevention of contact with susceptible and latent individuals, and a control measure based on the medical testing/screening of new immigrants before they are allowed into the population. In [59] three control interventions are studied with the aim of reducing the number of latent and active infectious individuals: *distancing* control, representing the effort of reducing susceptible individuals that become infected, such as, isolation of infectious individuals or educational campaigns; *case finding* control applied to latent individuals; and *case holding* control for infectious individuals. In [5, 6] *case finding* and *case holding* control measures are proposed for the minimization of the number of active infected individuals. In [16] the authors propose optimal control strategies for reducing the number of individuals in the class of *the lost to follow up individuals*. In [47, 50], optimal strategies for the minimization of the number of active TB infectious and persistent latent individuals are proposed.

The study of optimal control strategies produce valuable theoretical results, which can be used to suggest or design epidemic control programs. Depending on a chosen goal (or goals), various objective criteria may be adopted [5]. Although the implementation of the control policies, suggested by the mathematical analysis, can be difficult, they can be a support for the public health authorities and simulation of optimal control problems applied to mathematical models may become a powerful tool in their hands (see [5] and references cited therein).

The manuscript is organized as follows. In Section 2 mathematical models for TB dynamics are reviewed. They form, after introduction of the control functions, the control system of the optimal control problems on TB epidemics under consideration. The models with controls are presented in Section 3. A general optimal control problem is formulated in Section 4, where we explain how to obtain the analytic expression for the optimal controls, using the Pontryagin minimum principle [36]. In Section 5 we recall the numerical methods used to compute the optimal controls and associated dynamics. The main conclusions, derived from the numerical simulations, are resumed. Finally, in Section 6, an example is given, illustrating the

effectiveness of the implementation of the control strategies on a TB control disease. We end with Section 7 of conclusions and future research.

2 Uncontrolled TB Models

Mathematical models have become important tools in analyzing the spread and control of infectious diseases [25]. In this section we present different mathematical TB models which are, after some modifications, the control system of optimal control problems on TB epidemics (see Section 3).

In an infectious disease model, the total population is divided into epidemiological subclasses. Some of the standard classes are: susceptible individuals (S), latently infected individuals (infected but not infectious) (E), infectious (I), and the recovered and cured individuals (R). Eight possible compartmental models, described by their flow patterns, are: SI , SIS , SEI , $SEIS$, SIR , $SIRS$, $SEIR$ and $SEIRS$. For example, in a $SEIRS$ model, susceptible become exposed in the latent period, then infectious, then recovered with temporary immunity and then susceptible again when the immunity wears off [25]. Here, we choose to denote the class of latently infected individuals by L and the class of recovered and cured individuals by T .

In [7] the authors present a $SEIRS$ model for TB. The latently infected and infectious individuals with typical TB are denoted by L_1 and I_1 , respectively. The model is given by

$$\begin{cases} \dot{S}(t) = \Lambda - \beta c S(t) \frac{I_1(t)}{N(t)} - \mu S(t), \\ \dot{L}_1(t) = \beta c S(t) \frac{I_1(t)}{N(t)} - (\mu + k_1 + r_1) L_1(t) + \sigma \beta c T(t) \frac{I_1(t)}{N(t)}, \\ \dot{I}_1(t) = k_1 L_1(t) - (\mu + r_2 + d_1) I_1(t), \\ \dot{T}(t) = r_1 L_1(t) + r_2 I_1(t) - \sigma \beta c T(t) \frac{I_1(t)}{N(t)} - \mu T(t), \end{cases} \quad (1)$$

where N denotes the total population, $N(t) = S(t) + L_1(t) + I_1(t) + T(t)$, Λ is the recruitment rate, β and $\sigma\beta$ are the probabilities that susceptible and treated individuals become infected by one infectious individual I_1 per contact per unit of time, respectively, c is the per-capita contact rate, μ is the per-capita natural death rate, k_1 is the rate at which an individual leaves the latent class L_1 by becoming infectious, d_1 is the per-capita TB induced death rate, and r_1 and r_2 are per-capita treatment rates for latent and infectious individuals, respectively. It is assumed that an individual can be infected only through contacts with infectious individuals.

In the same paper [7], a two-strain model is presented which considers resistant TB strain. Two subclasses of the total population are added: L_2 (latent) and I_2 (infectious), representing the developmental stages of resistant strains. It is assumed that I_2 individuals can infect S , L_1 and T individuals. The model is given by the following system:

$$\begin{cases}
\dot{S}(t) = \Lambda - \beta c S(t) \frac{I_1(t)}{N(t)} - \mu S(t) - \beta^* c S(t) \frac{I_2(t)}{N(t)}, \\
\dot{L}_1(t) = \beta c S(t) \frac{I_1(t)}{N(t)} - (\mu + k_1 + r_1) L_1(t) + \sigma \beta c T(t) \frac{I_1(t)}{N(t)} + p r_2 I_1(t) \\
\quad - \beta^* c L_1(t) \frac{I_2(t)}{N(t)}, \\
\dot{I}_1(t) = k_1 L_1(t) - (\mu + r_2 + d_1) I_1(t), \\
\dot{L}_2(t) = q r_2 I_1(t) - (\mu + k_2) L_2(t) + \beta^* c (S(t) + L_1(t) + T(t)) \frac{I_2(t)}{N(t)}, \\
\dot{I}_2(t) = k_2 L_2(t) - (\mu + d_2) I_2(t), \\
\dot{T}(t) = r_1 L_1(t) + (1 - p - q) r_2 I_1(t) - \sigma \beta c T(t) \frac{I_1(t)}{N(t)} - \mu T(t) - \beta^* c T(t) \frac{I_2(t)}{N(t)},
\end{cases} \quad (2)$$

with $N(t) = S(t) + L_1(t) + I_1(t) + L_2(t) + I_2(t) + T(t)$ and where β^* is the probability that treated individuals become infected by one resistant-TB infectious individual I_2 per contact per unit of time, d_2 and k_2 have similar meanings as d_1 and k_1 for resistant-TB, and $p + q$ is the proportion of those treated infectious individuals who did not complete their treatment. The proportion p modifies the rate that departs from the latent class, and $q r_2 I_1(t)$ gives the rate at which individuals develop resistant-TB due to an incomplete treatment of active TB. Therefore, $p \geq 0$, $q \geq 0$ and $p + q \leq 1$.

The results of [17] suggest that exogenous reinfection has a drastic effect on the qualitative dynamics of TB. If we introduce into model (1) the term $\rho \beta c L_1 I_1 / N$, which represents exogenous reinfection, we obtain the exogenous reinfection tuberculosis model developed in [17]. The parameter ρ represents the level of reinfection. A value of $\rho \in (0, 1)$ implies that reinfection is less likely than a new infection. In fact, a value of $\rho \in (0, 1)$ implies that a primary infection provides some degree of cross immunity to exogenous reinfections. A value of $\rho \in (1, \infty)$ implies that TB infection increases the likelihood of active TB. The authors take the conservative view that $0 < \rho < 1$ (see (6) in Section 3 for the model with controls).

In [35] a mathematical model is presented, which takes into account immigration of infectious individuals as well as isolation of the infectious individuals for treatment. The model without controls is an extension of that of [17]: one subclass of the total population, the class of isolated infectious individuals with typical TB, is added. The corresponding controlled model is given in Section 3, by (7).

In [5, 6, 16] fast and slow progression to the infectious class are considered and both models consider exogenous reinfection, chemoprophylaxis of latently infected individuals and treatment of active infected individuals. In [6] a *SEI* model is proposed, where the infective class is divided into two subclasses: diagnosed infectious (those who have an active TB confirmed after an examination in a hospital) and undiagnosed infectious (i.e., those who have an active TB but not confirmed by an examination in a hospital), denoted by I_1 and I_2 , respectively. The model in [6] is given by the following system of ordinary differential equations:

$$\begin{cases} \dot{S} = \Lambda - \beta \frac{I_1}{N} S - \mu S, \\ \dot{L}_1 = (1-g)\beta \frac{I_1}{N} S + r_2 I_1 + r_3 I_2 - (1-r_1)\sigma \lambda L_1 - [\mu + k_1(1-r_1)]L_1, \\ \dot{I}_1 = gf\beta \frac{I_1}{N} S + h(1-r_1)(k_1 + \sigma \beta \frac{I_1}{N})L_1 - (\mu + d_1 + r_2)I_1, \\ \dot{I}_2 = g(1-f)\lambda S + (1-h)(1-r_1)(k + \sigma \lambda)E - (\mu + d_3 + r_3)J, \end{cases} \quad (3)$$

where the fraction g of newly infected individuals are assumed to undergo a fast progression directly to TB, while the remainder is latently infected and enter the latent class L_1 . Among the newly infected individuals that undergo a fast progression to TB, a fraction f of them is detected, and will enter the diagnosed infectious class I_1 , while the remaining $1-f$ is undetected and will be transferred into the undiagnosed infectious class I_2 . In this model r_2 is the rate of effective per capita therapy of diagnosed infectious individuals I_1 . It is assumed that undiagnosed infectious individuals can naturally recover and will be transferred into the latent class L_1 at a constant rate $r_3 < r_2$. Here σ is the factor reducing the risk of infection as a result of acquiring immunity for latently infected individuals L_1 . Among latently infected individuals who become infectious, the fraction h of them is diagnosed and treated, while the remaining $1-h$ is not diagnosed and enters the undiagnosed infectious class I_2 . The parameter d_3 is the per capita TB induced death rate for undiagnosed infectious individuals. If we consider $f = 1$, $h = 1$, $r_3 = 0$ and $d_3 = 0$, then we obtain the model proposed in [5].

In [22] the authors present a model for TB that considers exogenous reinfection and post-exposure interventions. The class L_3 denotes the fraction of early latent individuals, that is, individuals that were recently infected (less than two years) and are not yet infectious; while L_4 denotes the class of persistent latent individuals who where infected and remain latent. The other classes are S , I_1 and T , with the same meaning has in the previous models. The model of [22] is given by the following system:

$$\begin{cases} \dot{S}(t) = \mu N - \frac{\beta}{N} I_1(t) S(t) - \mu S(t), \\ \dot{L}_3(t) = \frac{\beta}{N} I_1(t) (S(t) + \sigma L_4(t) + \sigma_R T(t)) - (\delta + \tau_1 + \mu) L_3(t), \\ \dot{I}_1(t) = k_1 \delta L_3(t) + \omega L_4(t) + \omega_R T(t) - (\tau_0 + \mu) I_1(t), \\ \dot{L}_4(t) = (1-k_1) \delta L_3(t) - \sigma \frac{\beta}{N} I_1(t) L_4(t) - (\omega + \tau_2 + \mu) L_4(t), \\ \dot{T}(t) = \tau_0 I_1(t) + \tau_1 L_3(t) + \tau_2 L_4(t) - \sigma_R \frac{\beta}{N} I_1(t) T(t) - (\omega_R + \mu) T(t). \end{cases} \quad (4)$$

Here σ has the same meaning has in the model (3) but applies to persistent latent individuals, L_4 , and σ_R represents the same parameter factor but for treated patients; δ denotes the rate at which individuals leave the L_3 compartment; ω is the rate of endogenous reactivation for persistent latent infections (untreated latent infections); ω_R is the rate of endogenous reactivation for treated individuals (for those who have undergone a therapeutic intervention); τ_0 is the rate of recovery under treatment of active TB (assuming an average duration of infectiousness of six months); τ_1 and τ_2 apply to latent individuals L_3 and L_4 , respectively, and are the rates at which

chemotherapy or a post-exposure vaccine is applied. In this model it is assumed that the total population is constant, i.e., the rate of birth and death, μ , are equal and there are no disease-related deaths.

3 Controlled TB Models

The model (2) is the basis of the work developed in [27], where two control functions, u_1 and u_2 , are introduced, representing control strategies for the two-strain TB model. The control system is given by

$$\begin{cases} \dot{S}(t) = \Lambda - \beta c S(t) \frac{I_1(t)}{N(t)} - \mu S(t) - \beta^* c S(t) \frac{I_2(t)}{N(t)}, \\ \dot{L}_1(t) = \beta c S(t) \frac{I_1(t)}{N(t)} - (\mu + k_1 + u_1(t)r_1)L_1(t) + \sigma \beta c T(t) \frac{I_1(t)}{N(t)} \\ \quad + (1 - u_2(t))pr_2I_1(t) - \beta^* c L_1(t) \frac{I_2(t)}{N(t)}, \\ \dot{I}_1(t) = k_1L_1(t) - (\mu + r_2 + d_1)I_1(t), \\ \dot{L}_2(t) = (1 - u_2(t))qr_2I_1(t) - (\mu + k_2)L_2(t) + \beta^* c (S(t) + L_1(t) + T(t)) \frac{I_2(t)}{N(t)}, \\ \dot{I}_2(t) = k_2L_2(t) - (\mu + d_2)I_2(t), \\ \dot{T}(t) = u_1(t)r_1L_1(t) + (1 - ((1 - u_2(t))(p + q))r_2I_1(t) - \sigma \beta c T(t) \frac{I_1(t)}{N(t)} \\ \quad - \mu T(t) - \beta^* c T(t) \frac{I_2(t)}{N(t)}. \end{cases} \quad (5)$$

The control u_1 represents the fraction of typical TB latent individuals, L_1 , that is identified and put under treatment (to reduce the number of individuals that may be infectious). The coefficient $1 - u_2(t)$ represents the effort that prevents the failure of the treatment in the typical TB infectious individuals (to reduce the number of individuals developing resistant TB). When the control u_2 is near 1, there is low treatment failure and high implementation costs.

In [24] the authors consider the exogenous reinfection TB model presented in [17] and introduce a control which simulates the effect of exogenous reinfection, that is, they consider a fixed value for ρ , $\rho = 0.4$, and multiply the term $\rho \beta c L_1 I_1 / N$ by $1 - u$. The coefficient $1 - u$ represents the effort that prevents the exogenous reinfection in order to reduce the contact between the infectious and exposed individuals, thus decreasing the number of infectious individuals. The exogenous reinfection TB model with control, proposed in [24], is given by

$$\begin{cases} \dot{S}(t) = \Lambda - \beta c S(t) \frac{I_1(t)}{N(t)} - \mu S(t), \\ \dot{L}_1(t) = \beta c S(t) \frac{I_1(t)}{N(t)} - p\beta c(1 - u(t))L_1(t) \frac{I_1(t)}{N(t)} - (\mu + k_1)L_1(t) + \sigma\beta c T(t) \frac{I_1(t)}{N(t)}, \\ \dot{I}_1(t) = p\beta c(1 - u(t))L_1(t) \frac{I_1(t)}{N(t)} + k_1 L_1(t) - (\mu + r_2 + d_1)I_1(t), \\ \dot{T}(t) = r_2 I_1(t) - \sigma\beta c T(t) \frac{I_1(t)}{N(t)} - \mu T(t), \end{cases} \quad (6)$$

with $N(t) = S(t) + L_1(t) + I_1(t) + T(t)$.

In [35] the model takes into account immigration of infectious individuals as well as isolation of the infectious for treatment. Two control functions are considered: u_1 and u_2 . The control u_1 accounts for medical testing/screening of new immigrants, before they are allowed into the population, while the coefficient $1 - u_1$ is the effort that sustains such a testing policy. The control u_2 is a *case finding* control that represents the fraction of active individuals that are identified and will be isolated in a special facility, like a hospital, for effective treatment and prevention of contacts with susceptible and latent individuals. Hence, the term $1 + u_2$ represents the effort that sustains the isolation policy. The model with controls is given by

$$\begin{cases} \dot{S} = \Lambda^* + (1 - (1 - u_1(t))(p^* + q^*))A - \beta c S \frac{I_1 + I_2}{N} - \mu S, \\ \dot{L}_1 = (1 - u_1(t))p^*A + (1 - m)\beta c S \frac{I_1 + I_2}{N} - p\beta c L_1 \frac{I_1 + I_2}{N} + \sigma\beta c T \frac{I_1 + \sigma J}{N} \\ \quad - (k_1 + \mu)L_1, \\ \dot{I}_1 = (1 - u_1(t))q^*A + m\beta c S \frac{I_1 + I_2}{N} + p\beta c L_1 \frac{I_1 + I_2}{N} + k_1 L_1 - (\mu + d_3 + r_2)I_1 \\ \quad - (1 + u_2(t))\xi I_1, \\ \dot{J} = (1 + u_2(t))\xi I_1 - (r_3 + \mu + d_4)J, \\ \dot{T} = r_2 I_1 + r_3 J - \sigma\beta c T \frac{I_1 + \sigma J}{N} - \mu T. \end{cases} \quad (7)$$

The constant A represents the number of new members arriving into the population, per unit of time; p^* is the fraction of A arriving infected with latent TB; and q^* is the fraction of A arriving infected with active TB, so that $0 \leq p^* + q^* \leq 1$. It is assumed that $1 - (p^* + q^*)A$ individuals are free from the disease. The parameter Λ^* is the recruitment rate. Here the population is replenished from births and immigration; d_3 and d_4 are the typical TB-induced mortality rates for active TB individuals, that were not isolated from the population, and for isolated TB cases, respectively; r_3 is the treatment rate for isolated infectious individuals. The parameter l is the isolation level and lies in the range $0 \leq l \leq 1$, where $l = 0$ indicates absolute isolation for active infectious TB cases and $l = 1$ indicates no effective isolation. The parameter $0 \leq \sigma^* \leq 1$ determines the level of contact that treated individuals have with isolated individuals. The authors assume that $\sigma^* < l$ and that the treated individuals have a reduced contact with the isolated infectious group, as some of the treated individuals are from the J class. By m , $0 < m < 1$, it is denoted the fraction of persons with new infections who develop to TB fast, per unit of time, while ξ is the rate of isolation.

The parameters μ , β , c , $\sigma\beta$, k_1 , p , σ and r_2 , have the same meaning as in the previous models (see Table 1).

Symbol	Description
Λ	Recruitment rate
μ	Per-capita natural death rate
b	Effective birth rate
d_1	Per-capita typical TB induced death rate
d_2	Per-capita resistant TB induced death rate
β	Rate at which susceptible individuals become infected by an infectious individual with typical TB
β^*	Rate at which susceptible individuals become infected by one resistant-TB infectious individual
$\sigma\beta$	Rate at which treated individuals become infected by an infectious individual with typical TB
c	Per-capita contact rate
k_1	Rate of progression to active TB
k_2	Rate of progression to active resistant TB
r	Per-capita treatment rate
r_1	Treatment rate of individuals with latent typical TB
r_2	Treatment rate of individuals with infectious typical TB
r_3	Treatment rate of undiagnosed infectious individuals
$1 - s$	Treatment success rate
p	Level of exogenous reinfection
$u + v$	Proportion of treated infectious individuals who did not complete their treatment
g	Fraction of newly infected individuals that undergo a fast progression to the infectious class
f	Fraction of newly infected individuals that undergo a fast progression to TB
h	Fraction of infectious individuals that are diagnosed and treated
σ	Factor reducing the risk of infection as a result of acquiring immunity for latently infected individuals
σ_R	Factor reducing the risk of infection as a result of acquiring immunity for treated individuals
δ	Rate at which individuals leave L_3 compartment
α	Non-progress rate from L_1 to I
ω	Rate of endogenous reactivation for persistent latent infections
ω_R	Rate of endogenous reactivation for treated infections
τ_0	Rate of recovery under treatment of active TB
τ_1	Rate of recovery under treatment of latent individuals L_3
τ_2	Rate of recovery under treatment of latent individuals L_4
N	Total population

Table 1: Parameters that are used in the mathematical models for TB transmission (with and without controls).

In [59] the authors modified a model from [2] in order to study the transmission dynamics for TB in South Korea in the forty years period from 1970 to 2009. The total population, N , is divided into susceptible individuals (S), high-risk latent (L_1) that are recently infected but not infectious, active-TB infectious (I) and permanently latent (L_5) with low risk. The main difference from the other TB mod-

els is the incorporation of time-dependent parameters. The birth and mortality rates are assumed as the time-dependent functions $b(t)$ and $\mu(t)$, respectively. The time-dependent function $k(t)$ is the per-capita rate of progression to active-TB from the recently latent class L_1 . Individuals who do not progress from the class L_1 to the class I and those who are treated in the class L_1 , are moved to the class L_5 at the per-capita rate α and $r(t)$, respectively. The time-dependent function $s(t)$ is the proportion of treated infectious individuals who did not complete their treatment; $1 - s(t)$ is the treatment success rate for active tuberculosis. As previously, the parameter β is the number of new infections with active-TB per unit of time. The authors propose optimal control treatment strategies of TB in South Korea, for the period from 2010 to 2030, for various possible scenarios. Since it is not feasible to have the mortality data or the total population data for the future, the authors used the averaged constant values from the year 2001 to 2009 instead of using $b(t)$, $\mu(t)$, $s(t)$ and $r(t)$. The estimated time-dependent $k(t)$ from the year 1970 to 2009 is, however, used to find the optimal treatment strategy for the future. Three time-dependent controls are introduced into the TB system. The control $u_1(t)$ is the *distancing control* and the coefficient $1 - u_1(t)$ represents the effort of reducing susceptible individuals that become infected by infectious individuals, such as isolation of infectious people or educational programs/campaigns for healthy control. The *case finding* control, $u_2(t)$, represents the effort of decreasing the number of individuals that may be infectious, such as identification through screening of latent individuals who are in high risk of developing TB and who may benefit from prevention intervention. The *case holding* control, $1 - u_3(t)$, represents the effort of reducing the reinfection individuals, such as taking care of patients until they complete their treatment. The control system is given by

$$\begin{cases} \dot{S}(t) = bN(t) - \mu S(t) - (1 - u_1(t))\beta \frac{S(t)}{N(t)}I(t), \\ \dot{L}_1(t) = (1 - u_1(t))\beta \frac{S(t)}{N(t)}I(t) - (k(t) + u_2(t)\alpha + \mu)L_1(t) + (1 - u_3(t))srI(t), \\ \dot{I}(t) = k(t)L_1(t) - (r + \mu)I(t), \\ \dot{L}_5(t) = (1 - (1 - u_3(t))s)rI(t) + u_2(t)\alpha L_1(t) - \mu I(t), \end{cases}$$

where $N(t) = S(t) + L_1(t) + I(t) + L_5(t)$.

In [5] the author formulates an optimal control problem where one control, u , is introduced in the TB model. The control represents the effort on the chemoprophylaxis parameter (r_1) of latently infected individuals to reduce the number of individuals that may develop active TB. The model with control is given by (3) with $1 - u_1r_1$ instead of $1 - r_1$ and considering $f = h = 1$ and $d_2 = r_3 = 0$. In [6], additionally to the control u_1 , a second control u_2 is included in the model (3), which represents the effort on detection (h) of infectious, to increase the treatment rate of infectious and, consequently, to reduce the number of infectious and the source of infection. The model with controls is given by (3) with $1 - u_1r_1$ instead of $1 - r_1$ and u_2h instead of h .

In [16] the authors propose a model adapted to Africa, in particular to Cameroon. A new class of individuals, called *the lost to follow up individuals*, is introduced. The individuals in this class are active infectious individuals who didn't take the treatment until the end, due to a brief relief of a long time treatment. Some of the lost to follow up individuals can transmit the disease without presenting any symptom. The authors present control measures for the reduction of the number of individuals that progress to the class of the lost to follow up individuals, L .

In [47, 50] two control functions, u_1 and u_2 , and two real positive constants, ε_1 and ε_2 , were introduced in the model (4). The control u_1 represents the effort in preventing the failure of treatment in active TB infectious individuals I_1 (*case holding*), and the control u_2 governs the fraction of persistent latent individuals L_4 that is put under treatment (*case finding*). The parameters $\varepsilon_i \in (0, 1)$, $i = 1, 2$, measure the effectiveness of the controls u_i , $i = 1, 2$, respectively, i.e., these parameters measure the efficacy of treatment interventions for active and persistent latent TB individuals, respectively. In [47] the model is applied to Angola.

In [27, 47, 50] it is assumed that the total population N is constant, that is, the recruitment rate is equal to μN , $\Lambda = \mu N$, and the TB induced death rates are equal to zero. In [5, 6, 16, 24, 35, 59] the total population is not considered to be constant.

4 Optimal Control Problems

The control strategies for the reduction of infectious and/or latent individuals imply a cost of implementation. This implementation cost depends on many factors, for example, costs for activities to facilitate *case holding*. Those activities can be challenging because of the fact that chemotherapy must be maintained for several months to ensure a lasting cure, but patients usually recover their sense of well-being after only a few weeks of treatment and may often stop taking medications [27, 39]. For *case finding*, the control policies consider actions for the prevention of disease development with preventive therapy of latently infected individuals, which can be done in different ways, for example, identifying TB cases where the first initiative patient/provider contact is taken by health providers (*active case finding*) or by the patient (*passive case finding*), and screening activities among population groups at high risk of TB (for example, immigrants from high prevalence countries) [27, 35]. The implementation cost is taken into account in the formulation of an optimal control problem and is mathematically traduced by a functional.

Let L and I denote the latent infected and infectious individuals, respectively, without any specific characteristic, and $u = (u_1, \dots, u_n)$, with $n \in \{1, 2, 3\}$ for the models described in Section 3, be the bounded Lebesgue measurable control function. Different cost functionals have been considered on the previously cited works on optimal control applied to TB models:

$$C_1(u) = \int_0^{t_f} \left[A_1 I(t) + A_2 L(t) + \sum_{i=1}^n \frac{B_i}{2} u_i^2(t) \right] dt,$$

$$C_2(u) = \int_0^{t_f} \left[A_1 I(t) + \sum_{i=1}^n \frac{B_i}{2} u_i^2(t) \right] dt,$$

and

$$C_3(u) = \int_0^{t_f} \left[A_2 L(t) + \sum_{i=1}^n \frac{B_i}{2} u_i^2(t) \right] dt.$$

It is assumed that the cost of the treatments are nonlinear and take a quadratic form. The coefficients, A_j , $j \in \{1, 2\}$, and B_i , $i \in \{1, 2, 3\}$, are balancing cost factors due to the size and importance of the three parts of the objective functional.

For the cost functional C_2 and C_3 , the aim is to minimize the infectious and latent individuals, respectively, while keeping the cost low. For the cost functional C_1 , both infectious and latent individuals are wished to be minimized, keeping the cost of control interventions low.

A cost functional of type C_1 is adopted by [27, 47, 50, 59], C_2 is chosen in [5, 6, 24, 35] and C_3 is the objective functional in [16].

Let (\mathcal{S}) denote a mathematical model for TB with controls (see Section 3) given by a finite number, m , of differential equations. Assume that the control system (\mathcal{S}) is given by $\dot{X} = f(X, u)$, where f is a Lipschitz continuous function with respect to the state variable X , $X \in \mathbb{R}^m$, on the time interval $[0, t_f]$ and $X(0) = X_0$ be the initial condition. Moreover, let $g(X, u)$ denote the integrand of the cost functional C under consideration and assume that g is convex with respect to the control u . The optimal control problem consists in finding a control u^* such that the associated state trajectory X^* is solution of the control system (\mathcal{S}) , in the time interval $[0, t_f]$ with initial conditions $X^*(0)$, and minimizes the cost functional C ,

$$C(u^*) = \min_{\Omega} C(u), \quad (8)$$

where Ω is the set of admissible controls (bounded and Lebesgue integrable functions) given by

$$\Omega = \{u \in L^1(0, t_f) \mid 0 \leq u_i \leq 1, i = 1, \dots, n\}.$$

According to the Pontryagin minimum principle [36], if $u^*(\cdot) \in \Omega$ is optimal for the optimization problem (8) subject to the control system (\mathcal{S}) with fixed initial conditions X_0 and fixed final time t_f , then there exists a nontrivial absolutely continuous mapping $\lambda : [0, t_f] \rightarrow \mathbb{R}^m$, called the *adjoint vector*, such that

$$\dot{X} = \frac{\partial H}{\partial \lambda} \quad (9)$$

and

$$\dot{\lambda} = -\frac{\partial H}{\partial X}, \quad (10)$$

where the function H defined by

$$H = H(X(t), \lambda(t), u(t)) = g(X(t), u(t)) + \langle \lambda(t), f(X(t), u(t)) \rangle$$

is called the *Hamiltonian*, and the minimization condition

$$H(X^*(t), \lambda^*(t), u^*(t)) = \min_{0 \leq u \leq 1} H(X^*(t), \lambda^*(t), u) \quad (11)$$

holds almost everywhere on $[0, t_f]$. Moreover, the transversality conditions

$$\lambda_i(t_f) = 0, \quad i = 1, \dots, m, \quad (12)$$

hold. This approach was considered in [6, 16, 24, 27, 35, 47, 59] for obtaining an analytic expression of the optimal control u^* . In [5] the analytical expression of the optimal control u^* is derived, using an algebraic approach, by solving a Riccati equation.

5 Numerical Methods and Simulations

In [27] the optimal treatment strategy is obtained by solving the optimality system, consisting of 12 ODEs from (5) and adjoint equations (10). An iterative method is used for solving the optimality system. The authors start to solve the state equations with a guess for the controls over the simulated time using a forward fourth order Runge–Kutta scheme. Because of the transversality conditions (12), the adjoint equations are solved by a backward fourth order Runge–Kutta scheme using the current iteration solution of the state equations. Then, the controls are updated by using a convex combination of the previous controls and the value from the characterizations derived by (11). This process is repeated and iteration is stopped if the values of unknowns at the previous iteration are close enough to the ones at the present iteration. The same numerical procedure is applied in [16, 35, 59]. In [47, 50] the authors use also the software IPOPT [61], the Matlab Optimal Control Software PROPT [63] and the algebraic modeling language AMPL [62]. See, for example, [1] for details on numerical simulations of optimal control applied to life sciences using Matlab. In [24] the authors apply a semi-implicit finite difference method developed by [23] and presented in [28]. For a gentle overview see [44].

In [27] different optimal control strategies are presented, which depend on the population size, cost of implementing treatment controls and the control parameters. The authors conclude that programs that follow the proposed control strategies can effectively reduce the number of latent and infectious resistant-strain TB cases. In [24] the numerical results show the effectiveness to introduce the control that prevents the exogenous reinfection, which reactivates the bacterium tuberculosis at the latent individuals. Analogously, in [5, 6] the results emphasize the importance of controlling exogenous reinfection using chemoprophylaxis and detection methods in reducing the number of actively infected individuals with tuberculosis. The numerical simulations in [35] show that the proposed control interventions can ef-

fectively reduce the number of latent and infectious TB cases. More precisely, the optimal control results show that a cost effective combination of screening/medical testing of immigrants, as well as isolation of infectious persons for treatment, may depend on cost of implementation of the controls and the parameters of the model, specially, the rate of isolation ξ , isolation level l , fraction of immigrants with latent TB p , and fraction of immigrants with active TB q .

6 Example: Optimal Control for the TB SEIRS Model

In this section we introduce a *case finding* control function u to the SEIRS mathematical model for TB (1) from [7]. The coefficient $1 - u(t)$ represents the effort that sustains the success of the treatment of latent individuals L_1 . We assume that the total population N is constant, that is, $d_1 = 0$. This assumption is appropriate when the time period is short or when the natural deaths or the immigration balances the emigration (see [25]).

The controlled model is given by (see Table 1 for the meaning of the parameters)

$$\begin{cases} \dot{S}(t) = \Lambda - \frac{\beta}{N}cS(t)I_1(t) - \mu S(t), \\ \dot{L}_1(t) = \frac{\beta}{N}cS(t)I_1(t) - (\mu + r_1)L_1(t) - (1 - u(t))k_1L_1(t) + \sigma\frac{\beta}{N}cT(t)I_1(t), \\ \dot{I}_1(t) = (1 - u(t))k_1L_1(t) - (\mu + r_2 + d_1)I_1(t), \\ \dot{T}(t) = r_1L_1(t) + r_2I_1(t) - \sigma\frac{\beta}{N}cT(t)I_1(t) - \mu T(t). \end{cases} \quad (13)$$

Our aim is to minimize the number of infectious individuals I_1 , while keeping the cost of control strategies implementation low, that is, (we choose a cost functional of type C_2 of Section 4)

$$C(u) = \int_0^{t_f} \left[AI_1(t) + \frac{B}{2}u^2(t) \right] dt. \quad (14)$$

In this example we propose to solve the optimal control problem that consists in finding a control u^* such that the associated state trajectory (S^*, L_1^*, I_1^*, T^*) is solution of the control system (13) in the time interval $[0, t_f]$ with initial conditions $(S(0), L_1(0), I_1(0), T(0))$ and minimize the cost functional C ,

$$C(u^*) = \min_{\Omega} C(u), \quad (15)$$

where Ω is the set of admissible controls given by

$$\Omega = \{u \in L^1(0, t_f) | 0 \leq u \leq 1\}.$$

Theorem 1. *The optimal control problem (13), (15) with fixed initial conditions $S(0)$, $I_1(0)$, $L_1(0)$ and $T(0)$ and fixed final time t_f , admits an unique solution*

$(S^*(\cdot), I_1^*(\cdot), L_1^*(\cdot), T^*(\cdot))$ associated to an optimal control $u^*(\cdot)$ on $[0, t_f]$. Moreover, there exists adjoint functions $\lambda_1^*(\cdot)$, $\lambda_2^*(\cdot)$, $\lambda_3^*(\cdot)$ and $\lambda_4^*(\cdot)$ such that

$$\begin{cases} \dot{\lambda}_1^*(t) = \lambda_1^*(t) \left(\frac{\beta}{N} c I_1^*(t) + \mu \right) - \lambda_2^*(t) \frac{\beta}{N} c I_1^*(t), \\ \dot{\lambda}_2^*(t) = \lambda_2^*(t) ((\mu + r_1) + (1 - u^*(t))k_1) - \lambda_3^*(t)(1 - u^*(t))k_1 - \lambda_4^*(t)r_1, \\ \dot{\lambda}_3^*(t) = -A + \lambda_1^*(t) \frac{\beta}{N} c S^*(t) - \lambda_2^*(t) \left(\frac{\beta}{N} c S^*(t) + \sigma \frac{\beta}{N} c T^*(t) \right) \\ \quad + \lambda_3^*(t)(\mu + r_2 + d_1) - \lambda_4^*(t) \left(r_2 - \sigma \frac{\beta}{N} c T^*(t) \right), \\ \dot{\lambda}_4^*(t) = -\lambda_2^*(t) \sigma \frac{\beta}{N} c I_1^*(t) + \lambda_4^*(t) \left(\sigma \frac{\beta}{N} c I_1^*(t) - \mu \right), \end{cases} \quad (16)$$

with transversality conditions

$$\lambda_i^*(t_f) = 0, \quad i = 1, \dots, 4.$$

Furthermore,

$$u^*(t) = \min \left\{ \max \left\{ 0, \frac{k_1}{B} L_1^*(t) (\lambda_3^*(t) - \lambda_2^*(t)) \right\}, 1 \right\}. \quad (17)$$

Proof. Existence of an optimal solution (S^*, L_1^*, I_1^*, T^*) , associated to an optimal control u^* , comes from the convexity of the integrand of the cost functional (14) with respect to the control u and the Lipschitz property of the state system with respect to state variables (S, L_1, I_1, T) (see, e.g., [10, 18]). System (16) is derived from the Pontryagin minimum principle (see (10), [36]) and the optimal control (17) comes from the minimization condition (11). The optimal control given by (17) is unique along all time interval due to the boundedness of the state and adjoint functions, the Lipschitz property of systems (13) and (16) and the fact that the problem is autonomous.

We end by presenting some numerical simulations with the following parameter values: $\mu = 0.0143$, $c = 1$, $\beta = 13$, $\sigma = 1$, $r_1 = 2$, and $r_2 = 1$ (see [7]). The initial conditions are: $S(0) = (76/120)N$, $L_1(0) = (38/120)N$, $I_1(0) = (5/120)N$, and $T(0) = (1/120)N$ (see [27]). We start showing that the implementation of the control has a positive impact on the reduction of infectious individuals. In Figure 1 we observe that the fraction of infectious individuals decreases significantly when control strategies are implemented. If our aim is to reduce the number of infectious individuals giving special attention to keep the cost of implementation of the control measures low, then the weight constant B should take bigger values than A . Take, without loss of generality, $A = 1$ and $B \geq 50$. In this case, we observe that the fraction of infectious individuals I_1/N and the optimal control u depend on the rate of progression to active TB (see Figure 2) and the size N of total population (see Figure 3). The period of time that the optimal control attains its maximum value increases with B (see Figure 4). However, contrary to what is desired, the fraction of infectious individuals starts increasing after some specific period of time. This can be avoided if the rate k of progression to active TB is low (see Figure 2), or if we

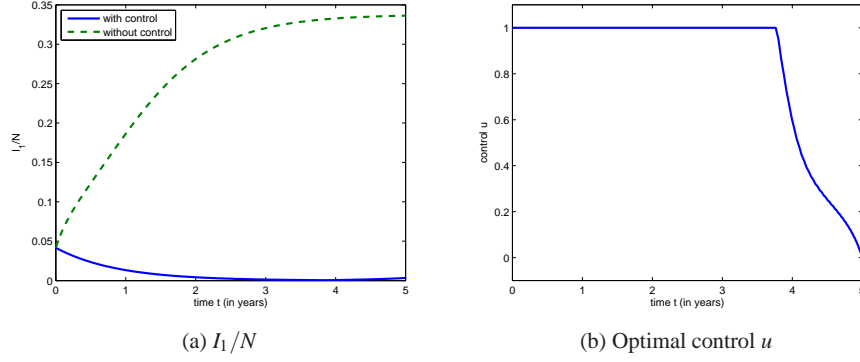


Fig. 1: Fraction of infectious individuals, with and without control, and optimal control (for $k_1 = 1$, $A = 1$, $B = 100$ and $N = 10000$).

give more importance to the decrease of the number of infectious individuals than to the cost of implementation of the control policies, that is, if we increase the value of the weight constant A . In fact, for $A \geq B$ the fraction of infectious individuals never increases in all treatment period, regardless the size of the population N or the value of k (see Figure 5). On the other hand, the optimal control attains the maximal value almost all the treatment period, which implies a higher cost implementation of control measures (see Figure 6).

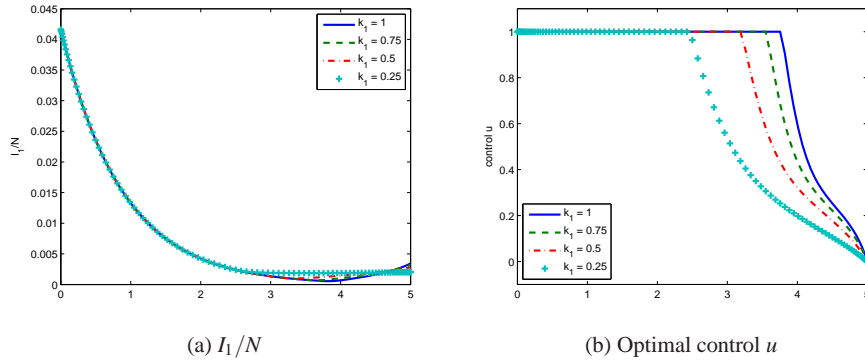


Fig. 2: Fraction of infectious individuals and optimal control for $k_1 \in \{0.25, 0.5, 0.75, 1\}$ (with $B = 100$, $A = 1$ and $N = 10000$).

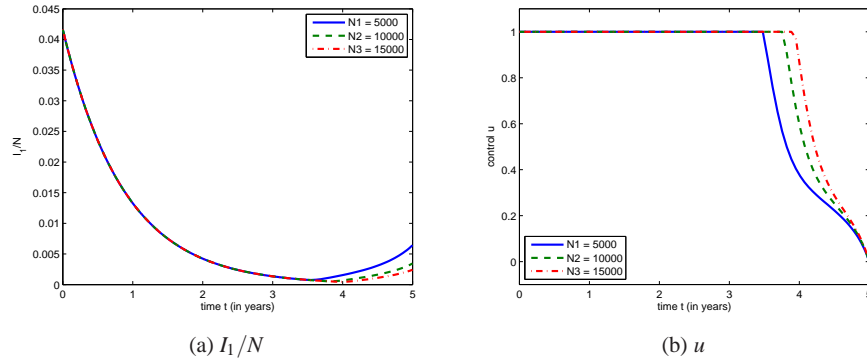


Fig. 3: Fraction of infectious individuals and optimal control for $N \in \{5000, 10000, 15000\}$ (with $B = 100$, $A = 1$ and $k_1 = 1$).

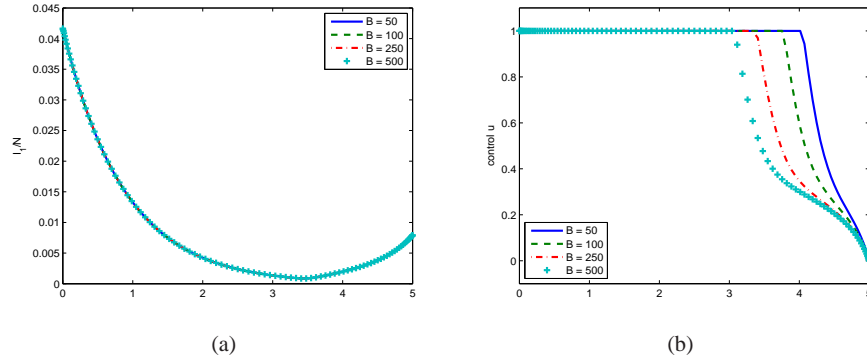


Fig. 4: Fraction of infectious individuals and optimal control for $B \in \{50, 100, 250, 500\}$ (with $A = 1$, $N = 10000$ and $k_1 = 1$).

7 Conclusion

A state of the art of uncontrolled and controlled mathematical models for tuberculosis (TB) has been presented. In particular, the paper reviews the works on optimal control of various models for the disease transmission dynamics of TB. Several results related to the dynamics and optimal control of TB have been reviewed and summarized. Two control strategies, “case finding” and “case holding”, are used to demonstrate the optimal control analysis.

The topics covered do not provide an exhaustive survey but rather an illustrative overview. For instance, a TB vaccine called BCG (Bacillus of Calmette and Guérin) has been used especially for children for several decades, and in some papers a dy-

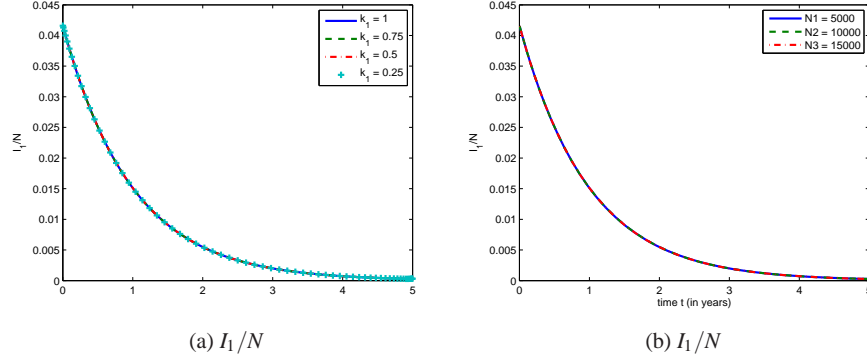


Fig. 5: Fraction of infectious individuals for $A = B = 100$ (with $k_1 \in \{0.25, 0.5, 0.75, 1\}$ and $N \in \{5000, 10000, 15000\}$).

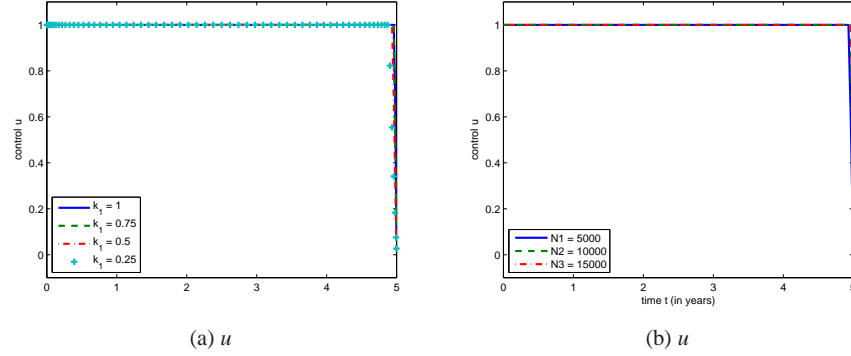


Fig. 6: Optimal control for $A = B = 100$ (with $k_1 \in \{0.25, 0.5, 0.75, 1\}$ and $N \in \{5000, 10000, 15000\}$).

namical system with vaccination has been formulated and analyzed (see, e.g., [9]), but the subject has not been covered here. The example provided (see Section 6) is also very simple: only a single-strain TB dynamics with SEIRS model is presented. The reader interested in a model to study the optimal control of a two-strain (drug-sensitive and drug-resistant) TB dynamics is referred to [27].

Current research includes the development of co-infection mathematical models for TB and human immunodeficiency virus (HIV) transmission dynamics [51]. The novelty of [51], with respect to available results in the literature, is considering both TB and acquired immune deficiency syndrome (AIDS) treatment for individuals with both infectious diseases. Results show that TB treatment for individuals with only TB infection reduces the number of individuals that become co-infected

with TB and HIV/AIDS, and reduces the diseases (TB and AIDS) induced deaths. They also show that the treatment of individuals with only AIDS also reduces the number of co-infected individuals. Further, TB-treatment for co-infected individuals in the active and latent stage of TB disease, implies a decrease of the number of individuals that passes from HIV-positive to AIDS. Application of optimal control to such combined TB-HIV/AIDS co-infection models poses a number of numerical challenges and is under investigation. This will be addressed in a forthcoming paper.

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